REMARKS

Restriction /Election

Applicants have cancelled the subject matter of Groups II-IV from the claims by cancelling one of the formulas of "A" and cancelling claim 5. Applicants do not concede the propriety of the requirement to restrict subject matter within claim 1. Although the non elected single subject matter has been cancelled from claim 1, applicants reserve the right to contest the restriction requirement and reintroduce the cancelled subject matter.

Claims 17-19 have been amended to define methods using conventional language. Applicants submit these claims should be made part of Group I and that claims 20-22 should be rejoined with Group I once allowable subject matter has been identified.

Claim Rejections -35 USC §112, 2nd paragraph

Claims 8-16

The examiners comments regarding the functional language in claims 8-16 are noted and appreciated. Claim 8 has been amended to define a medicament with a particular use. Claims 9-16 already define medicaments with a particular use. While compounds of formulas A, II, and III share an active ingredient and a common feature, the recitation of a particular use serves to exclude agents that would interfere with the particular use.

Claims 1-2, 6-16

The terms "Chapter I". "Chapter II", "Chapter III" and "Chapter IV" have been deleted.

To differentiate the three substituents "R^1" used in the formulas for "E", two have been renamed "R^1_{II}" and "R^1_{III}" and the third has been retained as "R^1".

With the cancellation of the non-elected subject matter defined by the third formula which was "A", there are no longer multiple definitions for Q_1, Q_2, Q_3 or Q_4.

Claim Rejections - 35 USC §102

Claims 1-4, 6-16

Applicants submit these claims are distinguished from the compounds of WO 03095420 by the provisos recited in the claim 1 for Q_1-Q_4, the definition of R^1_{II} and the definition of R^1_{III} such that there is no anticipation.

Regarding Formula A, for the provisos requiring, "when Q_1 and Q_4 are both methylene and R^3 is hydroxy, then R^2 is hydroxy, C_{1-6} alkoxy or C_{1-6} alkanoyloxy." In the compounds illustrated on page 10 of the office action, where R^3 is hydroxy, R^2 is hydrogen and **not** "hydroxy, C_{1-6} alkoxy or C_{1-6} alkanoyloxy" such that they do not anticipate any compounds.

For the compounds of formula A and II with the moiety R^1_{II}, this moiety (R^1_{II}) is cycloalkyl optionally fused by aryl. The compounds illustrated on page 10 of the office action do not have such groups for R^1_{II} and therefore, do not anticipate the compounds of formula A and II' with the moiety R^1_{II}.

The compound of the formula III have the moiety R^1_{III} bound directly to the carbonyl group and so they do not define ureas.

For the compounds of the non-elected subject matter, one of Q_1 -Q_3 is nitrogen. The compounds illustrated on page 10 of the office action do not have nitrogen in the tetrahydronaphthylene structure such that they do not anticipate compounds where A is the non-elected structure of the claims herein.

Claim Rejections - 35 USC §103

Claims 1-2, 6-16

The "tetrahydronaphthylene" compounds of claims 1-2 and 6-16 (formula (A)) have substituents or a nitrogen atom which are not shown or suggested by JP04178362 and JP 04178363 and are unobvious in view of these references.

It is alleged that replacing hydrogen of the tetrahydronaphthylene compounds of JP04178362 and JP 04178363 with a methyl group would be obvious. No evidence has been

cited which would lead one skilled in the art to either select any of the compounds cited by the examiner as a lead compound or to make the methyl substitution and expect a successful result. The art the examiner refers to for guidance and/or motivation for this substitution is unrelated to the art of tetrahydronaphthylene compounds. The examiner states that, "Aman et. al. teaches a class of compounds that are antifungala, acaricides, miticides." (Page 11 of the current office action) There is no motivation for one skilled in the art to select any of the compounds disclosed in Aman et al as lead compounds for manipulation to treat urinary disorders. Similarly, Pevarello, "teaches a class of compounds that were useful a cdk/cyclin inhibitors." (Page 17 of the current office action) One of ordinary skill in the art would expect that similar analogs of compounds disclosed in Aman et al or Pevarello would be useful in the same way as the compounds from which it was created but not, like in the present application, where the compound displays a different function. Therefore there is no motivation for one skilled in the art to select any of the compounds cited in the office action as a lead compound.

Even if a lead compound is selected from the art cited by the office action, one of ordinary skill in the art would not expect that substituting hydrogen for a methyl group would yield similar activities from the compound. In the pharmaceutical art, substituting a methyl group commonly yields a change in activity. In Shue HJ et al, the introduction of an alpha-methyl group improved potency and duration of in vivo activity. See Shue HJ et al, *Cyclic urea derivatives as potent NK1 selective antagonists. Part II: Effects of fluoro and benzylic methyl substitutions*. Bioorg Med Chem Lett. 2006 Feb 15; 16(4): 1065-9. Epub 2005 Nov.14. Also, in Kanekar M.G. et al, the methyl group is involved in the in vivo carcinogenesis. See Kanekar M.G. et al, *Effect of the substitution of 3-methyl group on the carcinogenic activity of 2-naphthylamine*, Proceedings: Plant Sciences vol. 65, num. 6 pg 257-266 June 1967. Therefore, substituting hydrogen substituents on the tetrahydronaphthylene compounds of JP04178362 and JP 04178363 would not be obvious.

In *Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 989, 90 U.S.P.Q.2d 1947 (Fed.Cir.(Del.) May 13, 2009) the court reviewed art more closely related to

the present application than the relevant art in *In Re Paquette* or *Ex parte Bluestone*. The court in *Teva* held that changing the mere position of a substituent can render a compound sufficiently distinct to be non-obvious if success would not be expected.

In addition, many of the claimed compounds are distinguished by more than replacing a hydrogen with a methyl group. The substituents R^2 and R^3 on the moiety A (which includes tetrahydronaphthylene derivatives) do not include methyl groups. The substituent R^1_{II} includes complex cyclic structures.

Also, claim 1 has been amended, further distancing the claim from the prior art. The compounds of formula II are cycloalkyl ureas, not an aryl urea like the cited references. The compounds claimed herein are not taught by there references. The compounds of formula III are not ureas and therefore, are not taught in the cited prior art.

In that the cited references and evidence relied on do not show all of the claimed features, a showing of prima facie obviousness has not been made and the rejection under 35 USC 103 should be withdrawn.

Claims 1, 6-16

Claims 1 and 6-16 are allegedly obvious in view of the tetrahydronaphthylene compounds of US 6863647 for the same reasons set forth for JP04178362 and JP 04178363. It is alleged that replacing a hydrogen of US 6863647 with a methyl group would be obvious. As with the rejection based on JP04178362 and JP 04178363, as argued above, the examiner cites no evidence within US 6863647 from which one skilled in the art would select a lead compound, or provide methyl substitution on these lead compounds. There is no evidence one skilled in the art would expect a compound of US 6863647 substituted by methyl to provide useful compounds. Also as discussed above, the compounds of claims 1 and 6-16 vary in structure from those of US 6863647 by more than a methyl group on the "tetrahydronaphthylene compounds." The tetrahydronaphthylene compounds with substitutents defined by R^2 and R^3 are not shown or suggested by US 6,863,647. The tetrahydronaphthylene compounds with substitutents defined by the complex cyclic structures of substituent R^1_{II} are also not shown or suggested by US 6,863,647.

In absence of evidence of these features, the rejection of claims herein under 35 USC 103 is unsupported and should be withdrawn.

Claims 1-3, 6-16

Claims 1-3, 6-16 are allegedly obvious in view of WO 9422807, combined with WO 9745111, Patani and WO 99 37607.

WO 9422807 and WO 9745111 each describe tetrahydronaphthylene compounds without any substituents. Patani is alleged to provide motivation to replace a hydrogen atom with a hydroxyl group and WO 9422807 allegedly shows that hydroxylation of the ion channel is known.

As discussed above with regard to the rejection under 35 USC 102 based on WO 03095420, the claimed compounds require more than substitution of the tetrahydronaphthylene compounds by a hydroxyl group.

Claim Rejections -35 USC §112, 1st paragraph

Claims 1-4, 6-16

It is acknowledged in the office action that the specification provides enablement for using compounds of "formula A," where R^1, R^4 or R is phenyl, benzyl, CH_2-pyridyl, 1,3-benzodioxolyl, tetrahydronaphthalene, isoxazole, dihydroindene, thiadiazole and indole which are substituted with halogen $-CF_3$, $-OCF_3$, phenyl, pyridine, pyridyloxy, alkoxy and alkyl.

With such a broad scope of compounds admittedly enabled and no evidence to refute any of the teachings within the specification, applicants submit the specification is objectively enabling for the full scope of compounds of formulas A, II, and III and thus, the rejection should be withdrawn.

No evidence has been presented that the specification fails to provide adequate guidance in the preparation of the full scope of compounds of formulas A, II, and III or the preparation of pharmaceutical compositions with such compounds, how to administer

pharmaceutical compositions with such compounds of formula A, II, and III or how to test such compounds for physiological activity related to treatment.

Since the structure of the claimed compounds is clearly defined by formula A, II, and III applicants maintain one of ordinary skill in art could synthesize these compounds without undue experimentation relying only on conventional methods known in the art. One skilled in the art would recognize the appropriate starting materials necessary to prepare the claimed compounds without undue experimentation and without any guidance from the specification. No evidence has been presented to the contrary.

As to using the claimed compounds, the specification is clearly objectively enabling in disclosing that the compounds have pharmacological activity (see for example the claims 8-16 with functional language).

The distinctions in chemical properties between the compounds exemplified and those that have not bee exemplified do not diminish the enabling teachings within the specification. The examiner provides no basis why one skilled in the art could not make the full scope of compounds of formula A, II, and III , test the pharmacological activity of these compounds, prepare pharmaceutical compositions with these compounds, and administer these compounds.

The rejection of Claims 1-4, 6-16 is clearly deficient in general under controlling case law. The courts have placed the burden upon the PTO to provide evidence shedding doubt on the disclosure that the invention can be made and used as stated; see, e.g., In re Marzocchi, 439 F.2d 220, 169 U.S.P.Q. 367 (CCPA 1971) (holding that how an enablement teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance.) The disclosure must be taken as in compliance with the enablement requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein. See In re Marzocchi, supra. No such evidence or reason for doubting Applicants' disclosure has been provided. Only general statements and conclusions are made regarding the guidance provided with respect to the treatment of osteoporosis and inflammation.

For the reasons stated above, Applicants maintain that they have provided more than adequate guidance to enable the claimed invention and submit all pending claims meet the requirements of 35 U.S.C. §112, first paragraph.

Double patenting

Applicants will address the provisional rejections of Claims 1-4, 6-16 under the doctrine of obviousness type double patenting when allowable subject matter has been identified.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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Attorney Docket No.: BAYER-0176
Date: June 25, 2010